

REMARKS

Claims 1-13 are pending in this application. Claims 1-5 were previously canceled, leaving claims 6-13 remaining. Claims 6-9 have been amended.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found on page 4 to page 13; in claims 1-13 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Objection to the Specification

The Office Action objects to the Specification because the application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b).

Applicants respectfully traverse this objection. The application as filed, being the PCT publication WO99/30163, contains the Abstract of the Disclosure on the Bibliographic page of the published document. Thus, contrary to the Office Action, the application does contain an Abstract and is in full compliance with 37 CFR 1.72(b).

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection to the Specification.

**2. Rejection of Claims 6-13 under 35 U.S.C. §112,
first paragraph**

The Office Action rejects claims 6-13 under 35 U.S.C. §112, first paragraph relating to enablement. The examiner admits that the Specification is enabling for:

(1) A method for the preparation of a reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual, comprising: (a) obtaining blood samples from a number of individual, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof having a pI in the range of 6.5 to 9.5;

(2) A diagnostic method for determining schizophrenia in a subject comprising: (a) obtaining a blood samples from a subject and collecting platelets therefrom, (b) injecting said platelets into a subject and (c) examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of injection, a positive result being a reaction above that which is observed in non-schizophrenic subject, indicating that the subject has a high likelihood of being schizophrenic;

(3) A method for the preparation of a reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual comprising: (a) obtaining blood samples from a number of schizophrenic or nonschizophrenic individuals, preparing a pool from said samples and collecting platelets therefrom; (b) preparing a protein fraction from said platelet preparation comprising proteins or fractions thereof having a pI in the range of 6.5 to 9.5, (c) injecting said protein preparation into a subject and (d) examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of injection, a positive result being a reaction above that which is observed in nonschizophrenic subject, indicating that the subject has a high likelihood of being schizophrenic;

(4) A method for the preparation of a reagent for use in diagnosis of schizophrenia in an individual by detecting a DTH reaction in said individual following injection of said reagent to the individual comprising: (a) obtaining blood samples from an individuals and collecting platelets therefrom; (b) preparing a protein fraction therefrom from said platelet preparation comprising proteins or fractions thereof having a pI in the range of 6.5 to 9.5, (c) injecting said protein preparation into a subject and (d) examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of injection, a positive result being a reaction above that which is observed in non-schizophrenic subject, indicating that the subject has a high likelihood of being schizophrenic...

The Office Action rejects claims 6-13 because the Specification does not reasonably provide enablement for "any" methods as set forth in claims 6-13 for diagnosis of schizophrenia in an individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the following reasons:

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a diagnostic method for determining schizophrenia in a subject comprising the

steps of obtaining blood sample from a subject, preparing a pool of platelets from said subject, injecting said platelets or a proteins fraction from platelet having a pI in the range of 6.5 to 9.5 into a subject and examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of the injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject has a high likelihood of being schizophrenic.

The specification does not teach how to make and use any platelet proteins or fractions therefrom "having a pI of above about 6.5" for a diagnostic method of schizophrenia in a subject because the term "having" is open-ended. It expands the range of the pI at either or both ends of the platelet proteins or platelet protein fraction. In fact, the specification discloses that platelet proteins having a pI in the range of 2 to 6.5, referenced as pool 1, has no DTH response in schizophrenic patient (See page 13). Not only there are more than one platelet proteins associated with any one specific pI, there is insufficient guidance as to the molecular weight of any platelet proteins associated with that particular pI, let alone the structure associated with function of any platelet proteins for the claimed diagnostic method. A platelet protein without the molecular weight associated with the specific amino acid sequence has no structure, much less function.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Applicants have not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the various platelet proteins for the claimed method. While protein having a range of pI of above about 6.5 or a pI within the range of above 6.5 to about 9.5 may have some notion of the activity such as induces DTH, claiming a method of injecting platelet proteins fails to distinctly claim what that proteins are and what the compositions are made up of for the claimed method. Reasonable correlation must exist between the scope of

the claims and scope of enablement set forth. The specification does not describe nor enable any platelet proteins for the claimed diagnostic method other than the isolated platelet or platelet proteins fraction having a pI in the range of 6.5 to 9.5 as disclosed on page 12 of the specification.

Given the indefinite number of undisclosed platelet proteins having a pI of above about 6.5 or within the range of above 6.5 to about 9.5, it is unpredictable which undisclosed platelet proteins is useful for the claimed method of diagnosing schizophrenia in a subject. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants thank the Examiner for the acknowledgment of enablement of the subject matter described above, which is the subject matter of claims 10-13. The Examiner having admitted that claims 10-13 are enabled, Applicants further address only claims 6-9.

Examination begins with a thorough review of the application in its entirety and with a preliminary determination of the scope of the claims. The examiner must determine what the claims recite and determine the meaning of each claim **as a whole**. The first

analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when its parts are analyzed individually. (Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications).

Applicants respectfully traverse the rejection of claims 7-9 under 35 U.S.C. §112, first paragraph. The Examiner's analysis and comments appear to indicate a fundamental misunderstanding of the inventive subject matter. The Examiner in general confuses the requirements for patenting composition of matter claims, to a protein, with the requirements for patenting method of use claims to the **use** of a blood isolate. The claims are not directed to any characteristics of a specific composition, but to a blood platelet isolate in which the "how to make" and "how to use" requirements are fully satisfied (Specification pages 11-12: examples 1 and 2).

1. The Examiner states that "The specification discloses only a diagnostic method for determining schizophrenia in a subject comprising" the steps recited in each of the independent claims. Applicants submit that this statement clearly demonstrates the disconnect between the Examiner's understanding of the inventive subject and the Applicant's inventive disclosure and claims: the

specification discloses "only" a diagnostic method for determining schizophrenia in a subject because that **is** the claimed inventive subject matter. This application does not claim an isolated protein because that is **not** the inventive subject matter.

It is the **sole** province of the inventor to define the invention, not the Examiner, and the Examiner cannot require Applicants to claim a different invention simply because that is what she/he wants to examine. The argued "unpredictability" resulting from the failure to specifically identify which protein is the active agent misstates the claimed invention: the Examiner does not know that a single protein in the platelet isolate produces the DTH reaction, nor indeed even that the agent which produces the DTH reaction is a platelet protein at all. In any event, the identity of the precise agent which produces the DTH reaction is irrelevant, as such discovery constitutes an entirely separate invention which is different than the claimed inventive subject matter.

2. The Examiner states that "The specification does not teach how to make and use any platelet proteins or fractions therefrom 'having a pI of above about 6.5' for a diagnostic method of schizophrenia in a subject because the term 'having' is open-ended", and the term "about" is indefinite.

Contrary to the Office Action, the Federal Circuit has repeatedly made it abundantly clear that transitional phrases such as "having" must be interpreted in light of the specification to determine whether open or closed claim language is intended (See, e.g., Lampi Corp. v. American Power Products Inc., 228 F.3d 1365, 1376, 56 USPQ2d 1445, 1453 (Fed. Cir. 2000); Crystal Semiconductor Corp. v. TriTech Microelectronics Int'l Inc., 246 F.3d 1336, 1348, 57 USPQ2d 1953, 1959 (Fed. Cir. 2001); and Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1573, 43 USPQ2d 1398, 1410 (Fed. Cir. 1997)). In the context of a polynucleotide or polypeptide having a particular sequence as found in U.C. v. Lilly, the term "having" permits inclusion of other moieties and the term may be open-ended. However, as discussed throughout this Response, a polynucleotide or polypeptide having a particular sequence is **not** the inventive subject matter. In the present case, "having a pI of above about 6.5" refers to a required characteristic of the platelet fractions used in the inventive methods.

In order to advance prosecution, Applicants have amended the phrase "said proteins or fractions having a pI of above about 6.5" to now read "wherein the pI of said proteins or fractions is greater than or equal to about 6.5". This is an non-substantive and non-limiting amendment which Applicants consider purely semantic, in order to make clear that in this context, "above about

6.5" is not open-ended. As the Examiner has pointed out, Applicants' data shows that the fraction below a pI of 6.5 is inactive; thus, it is clear that the Examiner in fact does understand that the claim is not directed to subject matter below the "above about 6.5" threshold, and the claim language is not open-ended at the lower end of the range.

Example 1 discloses that a platelet fraction not subject to isoelectric focusing, i.e. not limited by any pI range, nevertheless has function. This disclosure would support claims having no pI limitation, had Applicants elected to make such claims. In a preferred embodiment shown in Example 2, Applicants found that the fraction having a pI below about 6.5 has no activity, leading Applicants to eliminate the range below about 6.5 from their claims, and leaving the range "above about 6.5." Taken together, Examples 1 and 2 fully support the claimed range, and the Examiner has presented no evidence to show why Applicants should be restricted to only one embodiment and not the other. The range "above about 6.5" is fully enabled.

3. The Examiner states that "Applicants have not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the various platelet proteins for the claimed method". From this the Examiner concludes that "claiming a method of injecting

platelet proteins fails to distinctly claim what that proteins are and what the compositions are made up of for the claimed method".

Again, the Examiner misstates the inventive subject matter. This application does not claim "what that [sic; the] proteins are." This application claims, in relevant part, methods for using the product of a process: a composition isolated from blood by the steps of isolating a platelet fraction (a technique well known in the art for decades) and further isolating a part of the platelet fraction based on isoelectric focusing. As discussed above, the Examiner does not, and cannot, know that it is only one protein, or indeed a protein at all, which provokes a DTH response; it may well be that multiple protein(s) and/or other factor(s), which co-isolate with pool 2 platelets, are required to produce the DTH response. What is claimed is the fraction produced by the inventive process, not a single component of that fraction.

The Federal Circuit and its predecessors have made it quite clear that the Examiner cannot require the kind of specificity demanded in the Office Action: by law, a patent application is presumptively enabled when filed. "As a matter of Patent Office practice...a specification...must be taken as in compliance with the enablement requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In re Marzocchi, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (CCPA 1971). The claims are actually more narrow than the disclosed examples. The Examiner has failed to show **any** evidence that the platelet isolate fully described in the application, and successfully tested, does not produce a DTH reaction in individuals subject to developing schizophrenia. In the absence of such evidence, there is no *prima facie* case of non-enablement and this rejection must be withdrawn. Applicants respectfully refuse to accept the Examiner's attempts to change their inventive subject matter.

4. The Examiner states that "it is unpredictable which undisclosed platelet proteins is [sic] useful for the claimed method of diagnosing schizophrenia in a subject. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention."

Applicants respectfully submit there is absolutely **no issue** of undue experimentation because there is **no experimentation whatsoever** required to practice the inventive subject matter. Applicants note that the Examiner has cited no evidence that any experimentation is required to practice the inventive subject matter. As clearly and completely described in the Specification and claims, one need only take a blood sample, isolate the platelet fraction, further isolate the fraction of the platelet fraction

having a pI above about 6.5, and then use that isolate in the inventive methods for determining schizophrenia; nothing more is required to make or use the inventive subject matter.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

**3. Rejection of Claims 6-13 under 35 U.S.C. §112,
first paragraph**

The Office Action further rejects claims 6-13 under 35 U.S.C. §112, first paragraph relating to written description for the following reasons:

The specification discloses only a diagnostic method for determining schizophrenia in a subject comprising the steps of obtaining blood sample from a subject, preparing a pool of platelets from said subject, injecting said platelets or a proteins fraction from platelet having a pI in the range of 6.5 to 9.5 into a subject and examining the subject for the occurrence of delayed type hypersensitivity reaction at the site of the injection, a positive result being a reaction above that which is observed in non-schizophrenic subjects, indicating that the subject has a high likelihood of being schizophrenic.

With the exception of the specific isolated platelet or platelet proteins fraction having a pI in the range of 6.5 to 9.5 for the claimed diagnostic method, there is insufficient written description about the structure associated with function of any platelet proteins having a pI of about 6.5, any platelet protein fraction having a pI of about 6.5, any platelet proteins have a pI within the range of above 6.5 to about 9.5 because there is written description about the structure associated with function such of any platelet proteins such as the molecular weight, amino acid composition, N-terminal sequence that distinctly identifies the various platelet proteins with that particular pI in the protein fraction

for the claimed method of diagnosis of schizophrenia in an individual.

Applicants thank the Examiner for the acknowledgment that the subject matter of claims 10-13 has sufficient written description.

Applicants limit their comments to claims 6-9.

Applicants respectfully traverse the reject under 35 U.S.C. §112, first paragraph for insufficient written description. The "written description" requirement requires the inventor to clearly convey to those skilled in the art, through the specification, that the applicant has invented the specific subject matter of the claims (In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976)). Although the applicant does not have to describe the subject matter claimed in the specification using exactly the same words used in the claims, the description must be sufficiently clear to allow one of ordinary skill to recognize that the applicant invented what is claimed (In re Lukach, 442 F.2d 967, 969, 169 USPQ 795, 796 (CCPA 1971); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). The essential goal of the description of the invention requirement is to clearly convey that an applicant has invented the subject matter which is claimed (In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977)), and to put the public in possession of what the applicant claims as the invention (Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir.

1997)).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention (See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116).

Possession may be shown in a variety of ways, including description of an actual reduction to practice. A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose (Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998)).

Only if the application does not describe either (1) an actual reduction to practice, or (2) reduction to drawings, or (3) chemical or other structural formula, as discussed above, should the Examiner consider further the sufficiency of the written description (Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001: comment 7, at page 1101, columns 1 and 2; discussion of "claim drawn to a single embodiment or

species" at page 1106, column 1, item 1(c)). The claim inventive subject matter relates to a single embodiment within the meaning of the Guidelines, is fully supported by an actual reduction to practice in Examples 1 and 2, and is thus fully supported for written description purposes.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph relating to written description.

**4. Rejection of Claims 6, 7, and 9 under 35 U.S.C. §112,
second paragraph**

The Office Action rejects claims 6, 7, and 9 under 35 U.S.C. §112, second paragraph, for the following reasons:

The "having a pI **above about** 6.5" in claims 6, 7 and 9 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

Applicants respectfully traverse the rejection under 35 U.S.C. §112, second paragraph because the rejection fails to state any facts about why or how the Examiner believes that the language "having a pI above about 6.5" is indefinite and ambiguous. Thus, the Examiner has failed to state a *prima facie* case of indefiniteness.

Without waiving this deficiency and in an effort to advance prosecution, Applicants construe this rejection to refer to the

highlighted words "above about" and the discussion found in the enablement rejection relating to the purported "open-endedness" of the pI range.

In order to advance prosecution, Applicants have amended the phrase "said proteins or fractions having a pI of above about 6.5" to now read "wherein the pI of said proteins or fractions is greater than or equal to about 6.5". This is an non-substantive and non-limiting amendment which Applicants consider purely semantic, in order to make clear that in this context, "above about 6.5" is not open-ended. However, while amended, the claims retain use of the term "about."

The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph (Seattle Box Co., v. Industrial Crating & Packing, Inc., 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984)). Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree (MPEP §2173.05(b)).

In examples 1 and 2, the Specification for the present application makes clear that (1) the pI range below about 6.5 is

non-functional and (2) the pI range was determined experimentally, using the instruments available to Applicants. It is well known in the art that experimental data is only accurate within the inherent range of error of the experimental procedures and instruments. Contrary to the Office Action, "about" is thus clear in light of the standard established in the Specification.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph.

5. Rejection of Claims 6-13 under 35 U.S.C. §103(a)

The Office Action rejects claims 6-13 under 35 U.S.C. §103(a) as being unpatentable over WO 97/13152 publication (of record, April 1997; PTO 1449) in view of Kessler, et al (of record, Dementia 6(6): 330-3, 1995; PTO 892), U.S. Patent No. 5,429,947 (July 1995, PTO 892), Burbaea, et al (of record, ZH Nevropatol Psichiatr IM S Korsakova 86(1): 103-105, 1986; PTO 1449) and Jankovic, et al (J Immunol 135(2 suppl): 583s-587s, Aug 1985, PTO 892). As the basis for this rejection, the Office Action states:

The WO 97/13152 publication (Shinitzky et al) teaches a diagnostic method comprising collecting blood from a number of individuals such as demented patients or healthy normal subjects, isolating platelet from the said blood samples (See entire document, page 8 in particular), collecting the platelets and preparing platelet proteins by isoelectric focusing, (See page 10) wherein said proteins have a pI between 7 and 9 which anticipates the claimed pI above about 6.5 as recited in

claim 6 (See page 12, Fig 4). The reference platelet protein having a pI of 9 is above the claimed pI above about 6.5 as recited in claim 8. Further the term "about" expands the claimed pI to read on the reference pI of the platelet proteins and the claimed platelet proteins appear to be the reference platelet proteins.

Kessler et al teach platelets triggers autoimmune events which are apparently involved in schizophrenia (See page 330, column 1, first paragraph, in particular) and the numbers of platelet dense granules and platelet cell size in schizophrenic patients increased compared with healthy non-schizophrenic control (See Abstract, page 331, column 2, Table 1, in particular). Kessler et al further teach that the number of dense bodies per platelet in schizophrenic patients is relatively the same as the Alzheimer type demented patient (See Tables 1 and 2, in particular) and the number of dense granules in platelets from schizophrenic and demented patients are significantly higher than non-schizophrenic young individual (See Table 1 and 2, in particular).

Burbaea et al relates to the body sensitization of patients to neurospecific proteins S-100 and 10-40-4 and the reference does not disclose determining schizophrenia in patient by injecting platelets into the patient and determining whether there is a DTH reaction at the site of the injection.

Jankovic et al teach diagnosis of schizophrenia in an individual by detecting a delayed type hypersensitivity reaction to a human brain S-100 protein that is also expressed in other tissue and the high incidence of positive skin DTH reaction to the reference protein in schizophrenia indicates that cell-mediated immune processes may be involved in schizophrenia (See abstract, in particular). The '947 patent teaches a method of screening schizophrenia in a subject by detecting the elevated levels of a protein such as proteins 127 and 128 having a 40,000 Mr and pi 5.7 and 5.9 respectively found in Alzheimer and schizophrenic patients (See column 7, lines 56, Fig 1, in particular). The term "about" expands the range of the pI to read on the reference pI. The '947 patent further teach that another protein such as a-2 haptoglobin having a molecular weight of 18,000 and a pI of 6.5 that is present in increased concentration in both Alzheimer's disease and schizophrenic patients (See 7,

lines 45-48, Fig 2AB, in particular). The elevated levels of the reference proteins are found predominantly in the blood that contains platelets (See column 4, lines 13-18, in particular) and are useful as markers for diagnosis of schizophrenia and dementia in Alzheimer (See claims 1-2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the brain S-100 protein as taught by Burbaea et al or Jankovic et al for the platelet proteins or platelet proteins fractions having a pI of about 6.5 to 9 as taught by the WO97/13152 publication or the various proteins having a pI above about 6.5 as taught by the '947 patent because Kessler et al teach platelets triggers autoimmune events which are apparently involved in schizophrenia (See page 330, column 1, first paragraph, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Burbaea et al teach the use of delayed type hypersensitivity reaction (DTH) for a diagnostic method for schizophrenia (See abstract in particular). Jankovic et al teach that cell mediated immune mechanism which can be determine by skin delayed reaction to any self protein such as brain S-100 protein or enolase is useful for diagnosis of schizophrenia. Kessler et al teach platelets triggers autoimmune events which are apparently involved in schizophrenia (See page 330, column 1, first paragraph, in particular) and the numbers of platelet dense granules and platelet cell size in schizophrenic patients increased compared with healthy non-schizophrenic control (See Abstract, page 331, column 2, Table 1, in particular). Kessler et al further teach that the number of dense bodies per platelet in schizophrenic patients is relatively the same as the Alzheimer-type demented patient (See Tables 1 and 2, in particular). The WO 97/13152 publication teaches platelet preparation comprising proteins or fractions thereof having a pI between 7 and 9. The '947 patent teaches elevated levels of the reference proteins such as 127, 128 and a-2 haptoglobin having a pI of about 6.5 is useful as markers for diagnosing schizophrenia and Alzheimer (See claims of '947 patent, in particular). The

platelet proteins in the claimed method appear to be the same reference proteins as taught by the references having an apparent pI above about 6.5 or within the range of above 6.5 to about 9.5 and the function of the references proteins such as inducing delayed type reaction is inherently properties of the reference proteins. Further, none of the instant claims recite a specific molecular weight associated with the claimed pI. Since the Patent Office does not have the facilities for examining and comparing the platelets proteins or fractions therefrom of the instant invention to those of the prior art, the burden is on applicant to show that the prior art proteins are different from the platelet proteins in the claimed method. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicants respectfully traverse this rejection. To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art reference must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Second, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Third, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Attached hereto, Applicants file the Declaration of Meir

Shinitzky, who is a co-inventor named in the present application, a co-inventor named in the cited WO 97/13152 application, a co-author of the cited Kessler, et al. (Dementia) publication, and as having personal knowledge of the work described in the cited Burbaea/Yankovich publication.

In the Declaration, Dr. Shinitzky describes in detail his own work relating to the cited WO 97/13152 application. In brief, WO 97/13152 shows that the 75 kD platelet-protein and the related platelet associated antibodies, which he disclosed in WO 97/13152 to be associated with multi-infarct dementia and dementia of the Alzheimer type, are not the same as the isolated platelet-proteins or fractions thereof having a pI above about 6.5, which are claimed in the present application. Contrary to the Office Action, WO 97/13152 teaches the use of different proteins for screening for a different disorder, and thus teaches nothing whatsoever about the claimed inventive subject matter.

Similarly, in the Declaration, Dr. Shinitzky describes in detail his own work relating to the cited Dementia publication. In brief, the Dementia publication shows a statistical correlation between the mean number of platelet dense granules and the incidence of schizophrenia in the experimental group, as well an inverse relationship between the mean number of platelet dense granules and the incidence of dementia. Contrary to the Examiner's conclusions in the Office Action, the Dementia publication teaches

away from any correlation between the number of platelet dense granules in schizophrenic patients and in Alzheimer-type demented patients.

In particular, as part of the work for the 1995 Dementia publication, Dr. Shinitzky and his colleagues did not isolate a platelet-protein or fraction thereof having a pI above about 6.5, did not inject anyone with a platelet-protein, and did not examine anyone for the presence or absence of a DTH reaction to anything. Thus, at the time of the Dementia publication in 1995, it was not obvious to one of ordinary skill in the art to use an isolated platelet-protein or fraction thereof having a pI above about 6.5 in a delayed-type hypersensitivity ("DTH") reaction assay, in a method of diagnosing the likelihood of an individual being schizophrenic.

Finally, in the Declaration, Dr. Shinitzky describes his personal knowledge of the work leading to the isolation of two new proteins from the brain tissues of deceased individuals by the principal investigator, Professor Yankovich, under whose direction Dr. Burbaea worked. In reviewing the data developed by Professor Yankovich and his co-workers, it is apparent that they showed IgG and IgM autoantibody activity, but no T cell involvement. Further, it is apparent that the observed hypersensitivity reaction was light mediated. Thus, despite the erroneous characterization by Burbaea of the observed reaction as a DTH reaction, the lack of T cell involvement and the light mediated character of the reaction

make it clear to one of ordinary skill in the art that Yankovich observed an immediate-type hypersensitivity reaction, not a DTH reaction.

Thus, in the absence of any teaching or suggestion in WO 97/13152 that the use of different platelet proteins for screening for a *different* disorder, dementia, the references cited lack any teaching of the use of a platelet-derived fraction for testing for **schizophrenia**. The other references do not remedy this deficiency, and the rejection lacks an essential element of the claims: any connection between detecting dementia with a platelet fraction, and detecting schizophrenia with anything. Thus, the claims of the present application cannot be obvious over 97/13152, alone or in combination.

Similarly, in the absence of any teaching or suggestion in the Dementia publication showing a correlation between the incidence of schizophrenia and the incidence of dementia relating to the mean number of platelet dense granules, there is no teaching in Kessler that platelets trigger autoimmune events involved in schizophrenia. Contrary to the Office Action, Kessler, shows just the opposite. Thus, the claims of the present application cannot be obvious over the Dementia publication, alone or in combination.

In the absence of any **reliable** teaching or suggestion in the Burbaea publication of a connection between a DTH reaction to the

identified brain proteins, or any other proteins, and schizophrenia, the references cited lack any teaching of any correlation of schizophrenia and DTH reactions. The other references do not remedy this deficiency, and the rejection lacks a second essential element of the claims: any connection between detecting schizophrenia and DTH reactions. Thus, the claims of the present application cannot be obvious over the Burbaea publication, alone or in combination.

Finally, Applicants address the Examiner's analysis of the '947 patent. The Examiner states that (1) "The reference pI of 5.7 and 5.9 is about the claimed pI of 6.5" and (2) "The elevated levels of the reference proteins are found predominantly in the blood **that contains platelets** (See column 4, lines 13-18, in particular)" (emphasis added).

For the reasons discussed in detail above, the term "about 6.5," if read fairly in relation to the Specification as a whole, clearly cannot include either 5.7 or 5.9. More troublesome, Applicants note with great dismay the Examiner's affirmative misrepresentation of the highlighted language from the '947 patent. In fact, the '947 patent says nothing about the platelet fraction of blood, and indeed does not even use the word "platelet" anywhere in the document. It does not appear from the record that this citation from the reference is accurate or a fair interpretation. Applicants respectfully request that the record be cleared of this

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misrepresentation.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be enabled, sufficiently described, and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of remaining claims 6-13 and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she/he has any questions or comments.

Respectfully submitted,

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